This Page Is Inserted by IFW Operations and is not a part of the Official Record

BEST AVAILABLE IMAGES

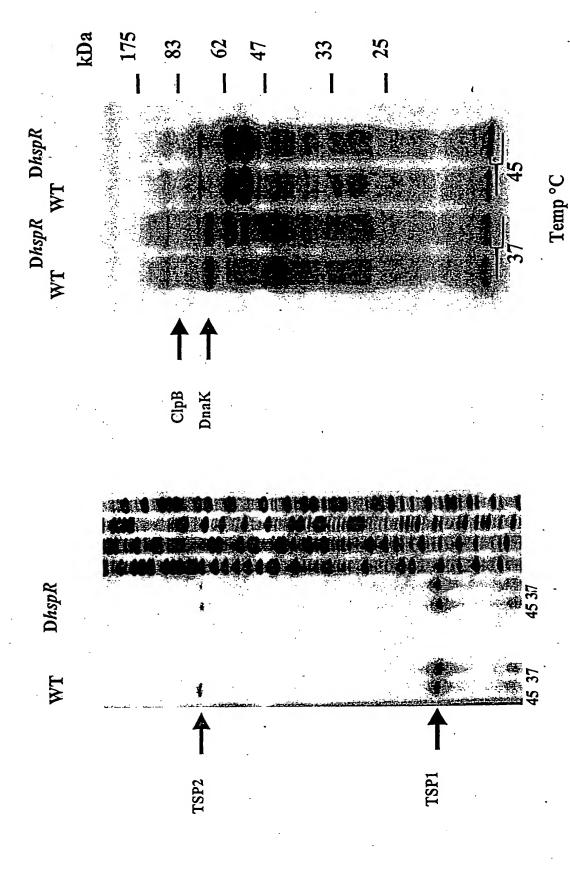
Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents will not correct images, please do not report the images to the Image Problem Mailbox.



Temp °C

1

48

Hours post-infection

°C (min)

Time at 53

Figure 3

Figure 4

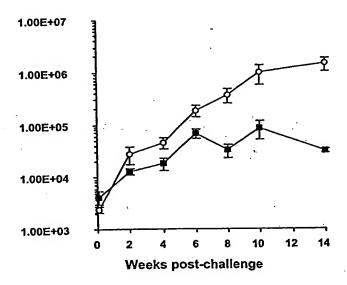
1.00E+07

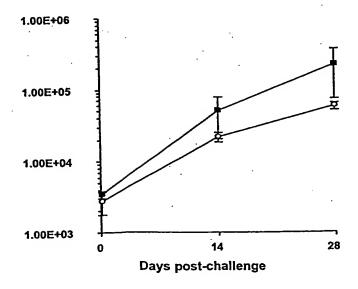
1.00E+06

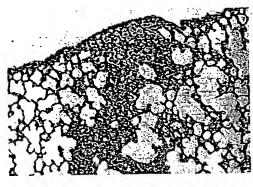
1.00E+05

0 2 4 6 8 10 12 14

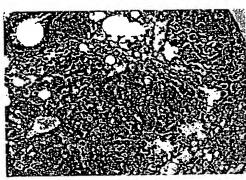
Weeks post-challenge



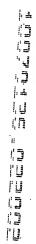


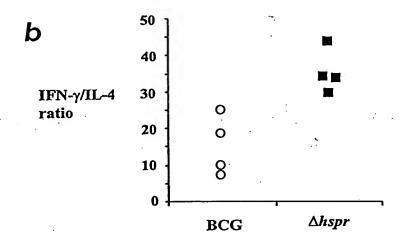


b



Last than the first that the first t





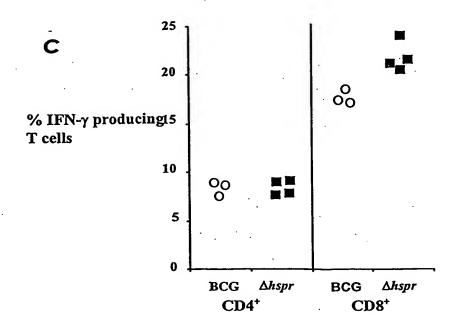
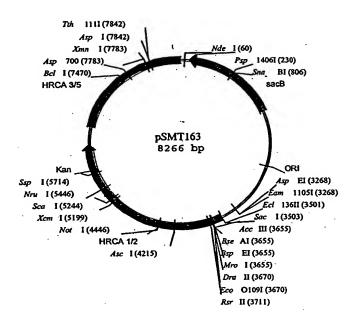
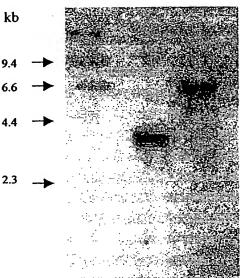


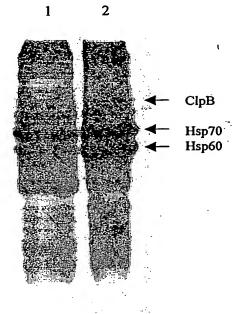
Figure 7. Counterselectable suicide vector for gene replacement of *hrca* in *M.tuberculosis* and *M.bovis* BCG.





2

'Figure 8. Southern blot of Kpn1 digested gDNA probed with HRCA1/HRCA2. Lane 1, hindIII digest of λ DNA; lane2, M.tuberculosis ΔhspR; lane 3, M.tuberculosis ΔhspR Δhrca.



Hsp10

Figure 9. SDS-PAGE showing overexpressed ClpB, Hsp70, Hsp60 and Hsp10 (GroES) in the hspR and hrca deleted strain. Lane 1, wild type M.tuberculosis H37Rv; lane 2, M.tuberculosis ΔhspR Δhrca.

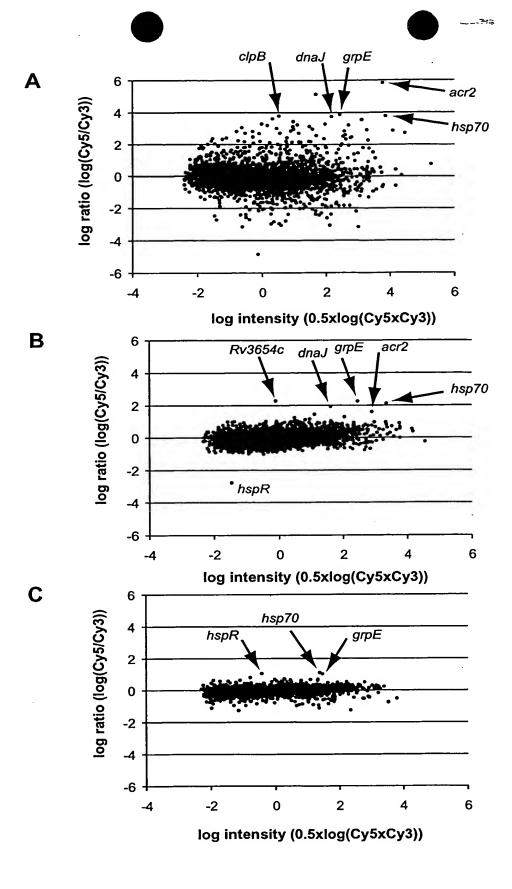


Figure 10

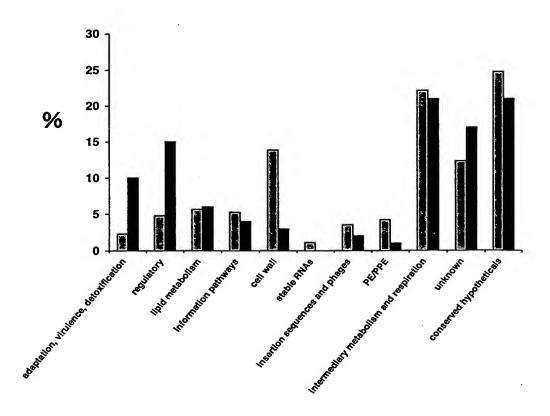


Figure 11

Α

```
AGGTGGAACTTAAGCGTGGTCGACTCAGGTTCTTGGT -61
acr2
        (Rv0251c)
                     CTCAGTAAGTTGAGTCCATCAGGTCAGGTCTGAATT -89
        (Rv0350)
hsp70
                     GAGGCAAGCTTGAGCGGGGTGGATCATAGTGCA -35
hsp70
        (Rv0350)
                     TGGGTAAAATTGAGCGGAACAGACTCAACATTGACGG -50
clpB
        (Rv0384c)
                           A--TTGAGCG----GACTCA-C-T-G
M.tb consensus HAIR
В
                     GAATAACGTTGECACTCGCCGACCGGTGAGTGCTAGGTCG -188
CGGGGCTTCTTGCACTCGCCATAGGCGAGTGCTAAGAAT -153
groEL2 (Rv0440)
groEL2 (Rv0440)
                     TAGCGGTTCTAGCACTTGAGACGGTAGAGTGCTAACGCC -23
Rv0991c
                     CTTGAGTGCTAGCACTGTCATGTATAGAGTGCTAGATGG -168
groES
        (Rv3418c)
                            T-CT-GCACTCG--A--G--GAGTGCTA
M.tb consensus CIRCE
```

Figure 12

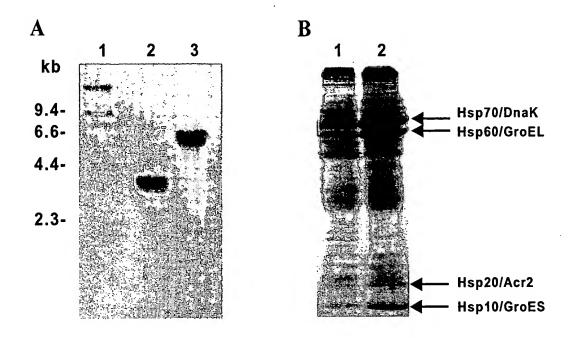


Figure 13

Gene designation	Gene name	P value	Fold change in \[\Delta h spR \) compared to wild-type	Fold change in the complemented strain, ΔhspR pSMT168, compared to wild-type	Regulatory sequence	Function
Rv0004		4.93E-03	2.77	1.19		СН
Rv0108c		4.12E-04	2.09	1.16		unknown
Rv0249c		1.06E-03	2.00	1.10	HAIR	membrane protein
Rv0250c		2.93E-05	2.26	1.15	HAIR	СН
Rv0251c	acr2	2.14E-07	2.54	1.11	HAIR	chaperone
Rv0268c		5.46E-03	1.96	1.23		unknown
Rv0291		7.37E-03	2.93	0.84		membrane protease
Rv0350	dnaK	2.49E-25	4.50	2.23	HAIR	chaperone
Rv0351	grpE	1.58E-28	4.99	2.12	HAIR	chaperone
Rv0352	dnaJ	1.40E-19	4.01	1.60	HAIR	chaperone
Rv0455c		3.89E-06	2.32	1.25		unknown
RV0469	umaA1	2.15E-04	2.06	0.98		mycolic acid synthesis
Rv0516c		1.19E-04	2.16	1.15		unknown
Rv0569		1.06E-03	1.98	0.62		СН
Rv0635		1.50E-04	2.13	1.05		СН
Rv0643c	mmaA3	5.09E-04	2.04	0.88		mycolic acid synthesis
Rv0655		9.26E-03	1.82	1.11	•	abc transporter
Rv0701	rplC	7.34E-03	1.95	1.27		ribosomal protein
Rv0714	rplN	2.55E-03	2.00	1.20		ribosomal protein
Rv0715	rplX	2.01E-03	2.03	1.10		ribosomal protein
Rv0909		1.90E-03	1.98	-		СН
Rv1078	pra	4.08E-04	2.00	1.09	•	СН
Rv1172c 6	•	2.27E-03	1.99	1.42		PE protein family
Rv1174c		2.90E-03	1.93	1.10		unknown
Rv1298	rpmE	4.64E-04	2.11	1.30	•	ribosomal protein
Rv1738		6.42E-07	2.46	0.89		СН
Rv1872c	IIdD2.	1.02E-03	1.93	1.14		oxidoreductase
Rv2005c		5.43E-04	2.03	0.83		universal stress protein
Rv2007c	fdxA	2.04E-14	3.17	0.86		ferredoxin
Rv2069	sigC	7.07E-03	1.94	1.16		sigma factor
Rv2094c	tatA	2.34E-04	2.17	1.15		protein translocase
Rv2137c		9.95E-04	1.97	1.09		- CH
Rv2185c		7.65E-04	2.07	1.02		СН
Rv2193	ctaE	2.05E-04	2.02	1.22		cytochrome-c-oxidase
Rv2288		6.64E-04	2.09	1.08		unknown
Rv2289	cdh	6.34E-03	1.87	1.03		cdp-diglyceride hydrolase
Rv2764c	thyA	8.29E-03	1.83	1.10		thymidylate synthase
Rv2816c	-	3.93E-10	2.84	1.59		СН
Rv2876		1.89E-03	1.90	1.20		unknown
Rv2960c		1.03E-03	2.04	1.04		unknown
Rv3101c	ftsX	3.61E-03	1.92	1.04		cell division protein
Rv3128c		2.12E-03	1.96	· 1.02		СН
Rv3407		1.44E-04	2.10	1.15		СН
	groES			1.06		chaperone
Rv3418c	•	4.45E-03	1.92	•		PE-PGRS protein family
Rv3508		9.24E-03	1.90	1.53		vnknown
Rv3654c		1.34E-27	5.08	1.12		
Rv3679		2.57E-03	1.96			anion transporter
Rv3680	LCD	5.91E-03	1.85	1.45		anion transporter
Rv3841	bfrB	7.64E-04	1.98	1.02		bacterioferritin

Figure 14

Rv0250c Rv0251c Rv0350	ppiA acr2	8.63E-04	wild-type		
Rv0251c Rv0350 Rv0351 Rv0352 Rv0440 Rv0455c Rv0464c Rv0469 Rv0705	acr2		1.80		peptidyl-prolyl cis-trans isomeras
Rv0350 Rv0351 Rv0352 Rv0440 Rv0455c Rv0464c Rv0469 Rv0705	acr2	9.78E-08	1.87	HAIR	СН
Rv0351 Rv0352 Rv0440 Rv0455c Rv0464c Rv0469 Rv0705		8.24E-05	1.88	HAIR	chaperone
Rv0352 Rv0440 Rv0455c Rv0464c Rv0469 Rv0705	dnaK/hsp70	2.32E-27	5.55	HAIR '	chaperone
Rv0440 Rv0455c Rv0464c Rv0469 Rv0705	grpE	1.52E-31	5.77	HAIR	chaperone
Rv0455c Rv0464c Rv0469 Rv0705	dnaj	1.71E-16	2.71	HAIR	chaperone
Rv0464c Rv0469 Rv0705	groEL2	5.32E-22	4.60	CIRCE	chaperone
Rv0469 Rv0705		2.15E-06	1.82		unknown
Rv0705		5.29E-03	1.60		СН
	umaA1	6.51E-06	1.81		mycolic acid synthesis
	rpsS	2.95E-07	1.93		ribosomal protein
K VU /UZ	rpmC	3.19E-03	1.65		ribosomal protein
Rv0979c		1.74E-04	1.75		unknown
Ry0991c		3.58E-08	1.95	CIRCE	СН
Rv1182	papA3	7.35E-03	1.73		pks-associated protein
Rv1185c	fadD21	7.82E-07	1.83		acyl-coA syhthase
Rv1233c		3.08E-03	1.68		СН
Rv1388	mIHF	4.73E-05	1.75		integration host factor
Rv1476		1.95E-03	1.60		membrane protein
Rv1642	rpmL	1.19E-05	1.83		ribosomal protein
Rv1721c	•	4.93E-03	3.10		СН
Rv17210		3.52E-03	1.60		PE protein family
Rv1860	modD/apa	1.11E-03	1.65	•	fibronectin-binding protein
Rv1980c	mpt64	1.89E-10	2.49		secreted unknown
Rv2069	sigC	3.85E-03	1.62		sigma factor
Rv2081c		5.05E-03	1.60		unknown
Rv2094c	tatA	1.16E-05	1.77		protein translocase
		2.09E-05	1.78		СН
Rv2185c		1.55E-08	1.78		unknown
Rv2271		2.02E-05	1.83		СН
Rv2302	frr				ribosome recycling factor
Rv2882c	tesA	2.49E-04	1.74 1.87		thioesterase
Rv2928	ppsA	1.14E-05			polyketide synthase
Rv2931	fadD28	7.16E-04	1.67		acyl-CoA synthetase
Rv2941	,	1.44E-06 1.70E-04	1.86		unknown
Rv2949c			1.67		oxidoreductase
Rv3224		2.82E-04	1.67		CH
Rv3281	lpqD	2.99E-03	1.60		secreted lipoprotein
Rv3390	groEL!	4.14E-03	1.63	CIRCE	chaperone
RV3417c	groES	1.19E-10	2.41	CIRCE	chaperone
Rv3418c	grota	8.22E-59	9.60	CIRCL	unknown
Rv3528c		4.16E-04	1.79		CH
Rv3615c		3.90E-03	1.65		unknown
Rv3654c		5.17E-40	3.97		excisionase
Rv3750c		1.25E-03	1.63		unknown
Rv3786c		4.01E-04	2.74		superoxide dismutase
Rv3846	sodA	5.24E-08	2.14		histone-like protein
Rv3852	hns	1.11E-04	1.69		•
Rv3874 Rv3891c		1.39E-04 7.12E-04	1.82 1.66		CH unknown

Figure 15